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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,793	05/30/2001	Stephen Joseph Vesper	VESPER1	5682

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EXAMINER
SHAHNAN SHAH, KHATOL S

ART UNIT	PAPER NUMBER
1645	8

DATE MAILED: 04/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/866,793	VESPER, STEPHEN JOSEPH	
	Examiner	Art Unit	
	Khatol S Shahnan-Shah	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *11 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-5 and 19-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendment A received January 11, 2002, paper 7 is acknowledged. Claims 1-2 and 6-18 were canceled without prejudice. New claims 19-21 were added.

2. Claims 3-5 and 19-21 are pending and under consideration.

Prior Citations of Title 35 Sections

3. The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior office action.

Objections Withdrawn

4. Objection to the specification made in paragraphs 4 of the office action mailed 9/135/2001, paper # 5 is withdrawn in view of applicant's amendment.

Rejections Maintained

5. Rejection of claims 3-5 under 35 USC 112- first paragraph made in paragraphs 5 of the office action mailed 9/135/2001, paper # 5 is maintained.

The rejection was as stated below:

Claims 3 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling *Stachybotrys chartarum*, does not reasonably provide enablement for other fungal species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/or the invention commensurate in scope with these claims. Enablement is considered in view of the Wands factors (MPEP) 2164.01(a). Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples (6) the quantity of experimentation, (7) the relative skill of those in the art, and (8) the breadth of the claims.

Claim 3 recites a method of detecting hemolysin-producing fungi. The scope of the claim encompass all hemolysin-producing fungi. Claim 5 recites a method of detecting hemolysin producing fungi for a group consisting of: *Stachybotrys chartarum, Aspergillus fumigatus, Candia albicans* and *Penicillium chrysogenum*. The scope of the claim encompass all of the above fungi. The specification teaches only isolation of *Stachybotrys chartarum* hemolysin (pages 6 and 7) and an ELISA assay for detecting *Stachybotrys chartarum* (page 8). The breadth of the claims are extremely broad, encompassing all hemolysin-producing fungi. The amount of direction or guidance is limited to the isolation and detection of hemolysin only from one fungal species (*Stachybotrys chartarum*). Because of the lack of guidance provided by the specification in regard to other hemolysins isolated from other hemolysin producing fungi, antibody production and their detection methods, it would require undue experimentation by one skilled in the art to make and/ or use the full claimed invention.

Applicant's arguments filed 10/01/2001 have been fully considered and are not persuasive. Applicant argues that " The present inventor has discovered that a number of fungal strains produce fungal hemolysins, and that these hemolysins can be isolated by using the culture supernatant or filtrate rather than a homogenate. This is important because the fungal hemolysins are glycosylated, secretory proteins, and the active form of this protein is in the culture filtrate/supernatant. These active fungal hemolysins can be used to determine if an organism has been exposed to the fungus, which produce the particular hemolysin. Once it had been discovered that it was possible to isolate active forms of hemolysins from fungi, one skilled in the art could easily extract hemolysins from fungi other than *Stachybotrys chartarum* and produce antibodies thereto without undue experimentation. Of course, those fungi that do produce hemolysins as a secretory protein are relevant. In fact, as can be seen from the attached Vesper et al. preprint, even some strains of *Stachybotrys* do not produce stachylysin under these conditions, which may make the threat of these non-producing strains to humans and animals

fundamentally different".

It is the examiner's position that the breadth of the claims are extremely broad, encompassing all hemolysin-producing fungi. The amount of direction or guidance is limited to the isolation and detection of hemolysin only from one fungal species (*Stachybotrys chartarum*). It is not clear from the instant disclosure how one can determine other fungal species that produce hemolysin. Even according to the applicant's own word "even some strains of *Stachybotrys* do not produce stachylysin under these conditions, which may make the threat of these non-producing strains to humans and animals fundamentally different". It is not clear what conditions applicant is referring to. Claim 3 also recites " hemolysin or active fragments thereof " The specification (pages 11 and 17) mentions modification of fragments by inclusion, deletion or modification of particular amino acid residues in a sequence. There is no guidance provided as to which sequence the applicant is referring to or which amino acid residues would be effective as immunogenic fragments. There is no guidance provided in the specification as how one would begin to choose these amino acids". Because of the above reasons and the lack of guidance provided by the specification in regard to other hemolysins isolated from other hemolysin producing fungi, antibody production and their detection methods, it would require undue experimentation by one skilled in the art to make and/ or use the full claimed invention.
The specification does not enable any person skilled in the art to which it pertains, or which it is most nearly connected, to identify or make the invention commensurate in scope with these claims.

6. Rejection of claims 3-5 under 35 USC 102(b) made in paragraphs 6 of the office action mailed 9/135/2001, paper # 5 is maintained.

The rejection was as stated below:

Claims 3-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Ishida et al. (Annual Report of Tohoku College of Pharmacy, No. 39, pp. 189-194, 1992).

Claims 3-5 are drawn to a method of detecting antigens to fungal hemolysins with labeled (enzyme, chemiluminescent) antibodies to fungal hemolysins.

Ishida et al teach a method of enzyme immunoassay of *Aspergillus* hemolysin by chemiluminescence reaction of Luminal-Peroxidase. They established a chemiluminescence enzyme immunoassay of *Aspergillus* hemolysin in which the enzyme immunoassay was carried out using peroxidase as a label enzyme by the double –antibody sandwich method. The results indicated that *Aspergillus* hemolysin could be determined accurately within the range of 10-100 pg by this method.

Applicant's arguments filed 10/01/2001 have been fully considered and are not persuasive. Applicant argues that what is significant about the present invention that these hemolysins can be isolated in the active form. Applicant also argues " There is absolutely nothing in Ishida et al. that teaches or even suggest that the Asp- hemolysin is obtained in the active form solely from the filtrate/supernatant".

It is the examiner's position that claims 3-5 are drawn to a method of detecting antigens to fungal hemolysins with labeled (enzyme, chemiluminescent) antibodies to fungal hemolysins. There is no recitation of hemolysin isolation in active form from the filtrate/supernatant and therefore applicant appears to argue limitations not recited in the claims.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 19-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining if a mammal has been exposed to *Stachybotrys chartarum*, does not reasonably provide enablement for other hemolysin-producing fungal species.

Enablement is considered in view of the Wands factors (MPEP) 2164.01(a). Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples (6) the quantity of experimentation, (7) the relative skill of those in the art, and (8) the breadth of the claims.

Claim 19 recites a method of detecting hemolysin-producing fungi. The scope of the claim encompasses all hemolysin-producing fungi. Claim 21 recites a method of detecting hemolysin producing fungi from a group consisting of: *Stachybotrys chartarum, Aspergillus fumigatus, Candia albicans* and *Penicillium chrysogenum*. The scope of the claim encompasses all of the above fungi. The specification teaches only isolation of *Stachybotrys chartarum* hemolysin (pages 6 and 7) and an ELISA assay for detecting *Stachybotrys chartarum* (page 8).

The role of hemolysins in virulence and diagnostic tests is well known in the art. Bacterial hemolysins such as purified *Vibrio vulnificus* hemolysin has been used in enzyme-linked immunosorbent assay to detect *Vibrio vulnificus* in environmental specimen (see Parker et al. 1995). A number of fungal pathogens produce hemolysins. These hemolysins have been

classified into five groups on the basis of different leakage patterns (see Ebina et al. page 148, 1994). *Aspergillus* hemolysin for example is classified in the group interacting with the specific receptor molecules in the membrane. However, no information is available yet to the nature of this hemolysin and others in the group (page 148, Ebina et al.). Stachylysin the hemolysin isolated from *Stachybotrys chartarum* looses hemolytic activity after dialysis or heat treatment (see abstract Vesper et al. 2001). *Candida albicans* a dimorphic fungi exhibits hemolytic activity when grown on glucose- enriched blood agar. This activity is present on intact organisms, and secreted into the culture medium (see Manns et al. 1994). Production of *Candida albicans* hemolytic factor (hemolysin) may be regulated by the presence of glucose in the growth medium (see page 5156 Manns et al. 1994).

Claim 19 also recites " hemolysin or active fragments thereof ". The specification (pages 11 and 17) mentions modification of fragments by inclusion, deletion or modification of particular amino acid residues in a sequence. There is no guidance provided as to which sequence the applicant is referring to or which amino acid residues would be effective as immunogenic fragments. There is no guidance provided in the specification as how one would begin to choose these amino acids".

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino

acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of prediction protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is **not** routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure.

One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. Multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins.

The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does **not** disclose the following:

- an amino acid sequence for the claimed protein;
- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;

- what fragments, if any, can be made which retain the biological activity if the intact protein; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicant have **not** provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the proteins structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Amgen Inc v. Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed.Cir.1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S.P.Q. 546(Bd. Pat. App. & Int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the invention commensurate in scope with the claims. The breadth of the claims are extremely broad, encompassing all hemolysin-producing fungi. The amount of direction or guidance is limited to the isolation and detection of hemolysin only from one fungal species (*Stachybotrys chartarum*). Because of the lack of guidance provided by the specification in regard to other hemolysins isolated from other hemolysin producing fungi, antibody production and their detection methods, it would require undue experimentation by one killed in the art to make or use the full claimed invention.
The amount of direction or guidance is limited to the isolation and detection of hemolysin only

from one fungal species (*Stachybotrys chartarum*). Because of the lack of guidance provided by the specification in regard to other hemolysins isolated from other hemolysin producing fungi, antibody production and their detection methods, it would require undue experimentation by one killed in the art to make or use the full claimed invention. The specification does not enable any person skilled in the art to which it pertains, or which it is most nearly connected, to identify or make the invention commensurate in scope with this claim

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall nclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 3-5 and 19-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear what applicants intend in recitation of "homiletical active fractions" in claim 21.

It is not clear what applicants intend in recitation of "active fragments thereof" in claims 3 and 21.

It is not clear what applicants intend in recitation of "detecting the label" in claims 3 and 21.

It is not clear what applicants intend in recitation of "synthetic medium" in claim 21.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishida et al. (Annual Report of Tohoku College of Pharmacy, No. 39, pp. 189-194, 1992) (prior art already made of record, Abstract only) in view of Fukuchi et al. (Biological Pharmacy Bulletin, Vol 19, No.4, pp. 547-550, 1996).

Claims 19-21 are drawn to a method of detecting antigens to fungal hemolysins with labeled (enzyme, chemiluminescent) antibodies to fungal hemolysins. The method steps comprising:

a) contacting a sample from the mammal with labeled antibodies

b) detecting the presence of antigens by detecting the labeled complex

Ishida et al. teach a method of enzyme immunoassay of *Aspergillus* hemolysin by chemiluminescence reaction of Luminal-Peroxidase. They established a chemiluminescence enzyme immunoassay of *Aspergillus* hemolysin in which the enzyme immunoassay was carried out using peroxidase as a label enzyme by the double –antibody sandwich method. The results indicated that *Aspergillus* hemolysin could be determined accurately within the range of 10-100 pg by this method (see abstract). Ishida et al. they do not teach specifically that the fungal hemolysin was isolated from the supernatant. Fukuchi et al. teach a method of isolation and purification of *Aspergillus* hemolysin by culturing a strain of the fungus on a synthetic medium (Sabouraud Medium), saturating the culture filtrate with ammonium sulfate to remove debris and isolating the hemolysin by column chromatography (see page 547).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of screening taught by Ishida et al. and the method of

purification taught by Fukuchi et al. to obtain the instant disclosure. Given the fact that use of purified proteins are important in diagnostic assays. One having ordinary skill in the art would have been motivated to obtain a better method to determine if a mammal has been exposed to a hemolysin producing fungus, which may have significant health implications.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol Shahnan-Shah whose telephone number is (703) 308-8896. The examiner can normally be reached on 7:30 AM - 4 PM from Monday through Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette F Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned to is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

4/5/04

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